#16
Attach

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BENNEKER et al.

Appl. No.: CPA of 09/200,743

Filed: November 27, 2000

For: CRYSTALLINE PAROXETINE METHANE SULFONATE (as amended)

Art Unit: 1625

Examiner: Chang, C.

DECLARATION OF THEODORUS HENDRICUS A. PETERS

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Theodorus Hendricus A. Peters, hereby declare as follows:

1. I am one of the applicants in the captioned patent application. The captioned application describes and claims *crystalline* paroxetine methane sulfonate and related pharmaceutical compositions and therapeutic methods of treatment.

2. Set forth below are facts which establish that the crystalline paroxetine methane sulfonate described and claimed in the captioned application is the same crystalline paroxetine methane sulfonate described and claimed in U.S. Patent 6,063,927.

My Technical Training And Experience

3. In 1984, I received a chemical laboratory engineering diploma (an "Ing" diploma, comparable to a Bachelors Degree) from the technical school OLAN (Arnhem, The Netherlands). In 1989, I received a diploma (equivalent to a Bachelor's Degree) in chemistry and in 1990 a general diploma (a "Drs." Diploma, comparable to a Master's Degree) in chemistry, both from the University of Utrecht (Utrecht, The Netherlands). In 1992, I completed the necessary coursework for my Ph.D., specializing in organic and organometallic chemistry, from the University of Utrecht. A copy of my CV is attached hereto as Tab A.

4. I have been engaged in pharmaceutical and chemical research since 1985. During this period, I have been employed by pharmaceutical and chemical companies, as well as by academic institutions. A significant part of my research has dealt with the synthesis of new pharmaceutical agents, including crystalline salts, and with the structural and physicochemical characterization thereof.

5. I am familiar with a variety of tests which may be used for ascertaining and/or comparing the identity and/or structure of crystalline pharmaceutical materials. These tests include, in particular, powder and single crystal x-ray diffraction ("XRD"), differential scanning calorimetry ("DSC"), solid state proton and carbon-13 nuclear magnetic resonance ("NMR"), infrared spectroscopy ("IR"), thermogravimetric analysis ("TGA") and mass spectroscopy ("MS").

6. I have regularly used many of the tests mentioned above to evaluate whether a given pharmaceutical material of interest could exist as different

crystalline "polymorphs." Polymorphism is the ability of a substance to exist as two or more structurally unique crystalline forms. Polymorphs of a given material have the same chemical composition, but they possess different three-dimensional crystal structures and they may exhibit different thermodynamic, spectroscopic, chemical and mechanical properties. Not all crystalline solids exist in different polymorphic forms.

7. In 1993, I joined Synthon BV ("Synthon"), the assignee of the captioned patent application. Initially, I held the position of head of Chemical Research and Development, in which capacity I was responsible for all R&D aspects in the chemistry of pharmaceutical projects. Presently, I am a Senior Scientist, in which capacity I am responsible for scientific and technical aspects of all pharmaceutical projects. My responsibilities have included investigating whether pharmaceutical materials of interest, for example those in R&D stage, exist in different crystalline polymorphic forms.

8. For the past seven years, my responsibilities have also included coordinating and managing patent-related matters, including patent applications and contested patent proceedings between Synthon and other parties.

The Synthon And SKB Patents

9. In my capacity as Synthon's patent coordinator, I am aware that Synthon and SmithKline Beecham ("SKB") have each received U.S. Patents which commonly disclose ***crystalline*** paroxetine methane sulfonate. The Synthon patent was applied for earlier and issued earlier than the SKB patent. The SKB patent, but not the Synthon patent, specifically claims "***crystalline***" paroxetine methane sulfonate.

10. Attached hereto as Tab B is a copy of Synthon's U.S. Patent 5,874,447 ("the '447 patent"). The '447 patent issued on February 23, 1999, from underlying application serial no. 08/872,023 (the " '023 application"), filed on June 10, 1997. The captioned application is a "continuing" application of the '023 application and the disclosure of the captioned application is the same as the disclosure in the '023 application.

11. Claim 21 of the '447 patent generically covers any form of paroxetine methane sulfonate, *i.e.*, amorphous, crystalline, dissolved, *etc.* Claim 24 of the '447 patent is directed to a pharmaceutical composition containing any form of paroxetine methane sulfonate and claim 28 is directed to a therapeutic method of treating depression and other disorders by administering a pharmaceutical composition containing any form of paroxetine methane sulfonate.

12. The claims of the captioned application are limited to <u>crystalline</u> paroxetine methane sulfonate, as well as related pharmaceutical compositions and therapeutic methods of treatment.

13. Attached hereto as Tab C is a copy of SKB's U.S. Patent 6,063,927 ("the '927 patent"). The '927 patent issued on May 16, 2000, from underlying application serial number 09/299,060, filed on April 23, 1999.

14. Claim 1 of the '927 patent is limited to "crystalline" paroxetine methane sulfonate. It recites eight allegedly "characteristic" IR peaks:

> Paroxetine methanesulfonate in crystalline form having the following characteristic IR peaks: 1603, 1194, 1045, 946, 830, 601, 554, and 539 ±4 cm^{-1}.

The Issue Of "Polymorphism" Raised By SKB

15. In my capacity as Synthon's patent coordinator, I am aware that during examination of a counterpart application of SKB's patent [Tab D], SKB asserted to the European Patent Office ("EPO") that the crystalline paroxetine methane sulfonate described in its application is a different "polymorph" of the crystalline paroxetine methane sulfonate described in a published (PCT) counterpart application of Synthon's patent. Tab E at 2. Initially, the EPO Examiner rejected SKB's argument. The EPO Examiner stated, "**a direct comparison of the [SKB] compound and the compound(s) disclosed in [Synthon]** would be required. Accordingly, the applicant is requested to submit suitable data, preferably showing the IR-spectra of either species alone **and in admixture** with each other." Tab F at 3, ¶ 3.3, original emphasis.

16. SKB never made the "direct comparison" requested by the EPO. SKB submitted copies of the complete IR spectra of the crystalline paroxetine methane sulfonates described in Examples 3 and 12 of its patent application, but it did not submit a complete spectrum of the crystalline paroxetine methane sulfonates described earlier by Synthon. SKB's declarant merely compared the *incomplete* list of IR peaks set forth in Table 1 of the Synthon patent with the selectively chosen and *incomplete* list of IR peaks set forth in SKB's claims. Tab G. SKB's attorney then argued that the claimed peaks "not found" in the Synthon Table 1 were "evidently" proof of a new crystalline form of paroxetine methane sulfonate [Tab H at 2]:

> Claim 1 of the present application stipulates that the crystalline methane sulfonate has at least the following IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554 and 539 ± 4 cm^{-1}.
>
> Even allowing for an error margin of ± 4 cm^{-1} (which is actually quite broad given the accuracy of modern IR spectrometers of about ± 1 cm^{-1}) only two of the above noted peaks are found in [Synthon's Patent Application] (namely at 1515 and 777 cm^{-1}).
>
> The remaining 8 (out of 10) peaks at 1603, 1194, 1045, 946, 830, 601, 554, and 539 cm^{-1} are not found in the material described by [Synthon] and are therefore evidently characteristic of a new crystalline form.

17. The prosecution history of SKB's '927 U.S. patent does not include any argument or evidence relating to the issue of polymorphism. Neither the '447 Synthon patent nor its published PCT counterpart was ever cited by the Examiner. In fact, no Office Action was ever issued. The file suggests, however, that SKB's attorney amended the original application claims in an attempt to distinguish the claimed crystalline paroxetine methane sulfonate from the crystalline methane sulfonate described in the '447 Synthon patent/PCT counterpart.

18. SKB's original U.S. application claims covered any physical form of paroxetine methane sulfonate, including crystalline and noncrystalline forms. Only some of the original application claims, not all, recited the (ten) IR peaks noted above. Tabs I and J. The original application claims were cancelled after filing and they were replaced by claims limited to crystalline paroxetine methane sulfonate having eight of the originally recited IR peaks. The new claims omitted recitation of the two IR peaks which are listed in Table 1 of the '447 Synthon patent. See Tab K. The '927 claims thus recite

only eight IR peaks, whereas SKB's original U.S. claims and the claims in SKB's EPO application recite ten IR peaks.

19. It appears, therefore, that SKB's '927 patent was permitted to issue solely because the eight IR peaks listed in its claims were not explicitly listed in the earlier Synthon patent. No evidence was ever submitted by SKB to establish that the crystalline materials described, respectively, by SKB and Synthon were in fact different.

20. Summarized below is evidence which establishes that SKB has *not* discovered or described a new or different crystalline polymorph of paroxetine methane sulfonate. First, Dr. Michael Crimmins has prepared crystalline paroxetine methane sulfonate in accordance with two different procedures described in the '447 Synthon patent and has confirmed that the powder x-ray diffraction pattern and infrared spectrum of those prepared materials are *identical* to the powder x-ray diffraction pattern and infrared spectrum of the crystalline paroxetine methane sulfonate described and claimed in the '927 SKB patent. Second, the '927 patent itself includes data which indicate that crystalline paroxetine methane sulfonate does not exist in polymorphic forms.

How Polymorphism Is Demonstrated

21. A conclusion that two or more crystalline materials are distinct polymorphic crystalline forms of a given material necessarily requires a comparison of those crystalline materials. A battery of tests has been used for such comparisons. These tests include: x-ray powder diffraction ("XRPD"); single-crystal x-ray diffraction ("XRD"); polarizing light microscopy ("PLM"); thermal analyses, such as differential scanning calorimetry ("DSC") and thermogravimetric analysis ("TGA"); vibrational

spectroscopy, such as infrared ("IR") and Raman; solid-state nuclear magnetic resonance ("NMR"); and solubility techniques.

22. Given the complexity and importance of the issues raised by the question of polymorphism, skilled scientists do not base a conclusion of polymorphism upon a single test. Rather, it is common practice to employ several tests. To do otherwise risks erroneous conclusions. See, for example, Threlfall, *Analysis Of Organic Polymorphs*, Analyst, Vol. 120 (1995) [Tab L at 2438]:

> All the solid state properties of the different polymorphic modifications of a compound will be different, but often only marginally so, to the point of instrumental indistinguishability. For this reason, it is important to look at potentially polymorphic systems by a variety of techniques to avoid erroneous conclusions. Failure to recognize a polymorph is the more obvious situation but it is also possible to identify polymorphs where none exist, if reliance is placed on too few techniques.

23. While many different physical tests may be used to compare known or suspected polymorphic forms of a particular pharmaceutical solid, the dispositive way of establishing the existence of different crystalline forms is to ascertain and then compare the crystalline structures of the materials in question. This is done by x-ray diffraction, either single crystal or powder. See Threlfall, Tab L at 2445, "In principle, then, any polymorph will give a distinctive x-ray powder pattern."

24. Because polymorphism depends upon the demonstrated existence of different crystalline structures, x-ray diffraction is generally regarded as the most useful analytical tool. See Byrn *et al.*, *Pharmaceutical Solids: A Strategic Approach To Regulatory Considerations,* Pharmaceutical Research, Vol. 12, No. 7 (1995) [Tab M at

946]: "The first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to answer the question: Are polymorphs possible? . . . . The solids produced are analyzed using x-ray diffraction and at least one of the other methods." See also Brittain, *Spectral Methods For The Characterization Of Polymorphs And Solvates*, Journal of Pharmaceutical Sciences, Vol. 86, No. 4 (1997) [Tab N at 405]:

> A complement of physical characterization methods have been developed for the study of polymorphs and solvates, with many workers choosing to use the classical methods of crystallography, microscopy, thermal analysis, and solubility studies. However, it must be emphasized that the defining criterion for the existence of polymorphic types is a nonequivalence of crystal structures. For pharmaceutical agents, this criterion requires that nonequivalent X-ray powder patterns are observed for the various forms. All other observations must be considered as supporting and ancillary information and cannot alone be taken as definitive proof of the existence of polymorphism.

25. Infrared spectroscopy ("IR") may sometimes be used to compare known or suspected polymorphic forms of a given material, but IR analysis alone is not regarded as dispositive of the question of possible polymorphism. IR is a type of vibrational spectroscopy. It provides information about the motion of functional groups in a crystalline solid. IR does not *per se* provide information about the three dimensional lattice structure of a crystalline solid. In addition, IR is subject to potentially significant variability which can give rise to inaccurate or incorrect conclusions.

26. The *United States Pharmacopeia* (*"USP"*) is internationally recognized in the pharmaceutical field as an authoritative compendium of quality standards and scientific tests, assays and analytical methods for characterizing,

identifying and/or comparing pharmaceutical materials. The USP acknowledges that infrared spectroscopy may be used in the evaluation of polymorphism, but it warns that recorded IR peak values "may vary by as much as 0.1 *um* or 10 cm^{-1}, depending upon the particular instrument used." See "Spectrophotometry and Light-scattering," Physical Tests <851>, *The United States Pharmacopeia*, 24th ed., page 1996, United States Pharmacopeial Convention, Rockville, MD, copy attached as Tab O. There are, in fact, numerous sampling and instrumental variables which should be carefully taken into account when using IR as a method for evaluating possible polymorphism. Some of these variables are summarized by Threlfall, *Analysis Of Organic Polymorphs* [Tab L at 2440]:

> . . . there are surprisingly few descriptions of the precautions to be taken when recording or interpreting the IR spectra of polymorphs. For example, in the case of non-matching spectra, a wide variety of causes might be suspected, including mis-labeling of a homologue, sample purity, crystal size, crystal habit and orientation, instability to comminution, formation or partial decomposition of a salt, solubility in the mulling medium, hydration, dehydration or other solvent loss under vacuum, level of impurities in the mulling or disk medium and instrumental variables including the inadequate elimination of background peaks. The latter can be a problem with the Fourier transform instruments now in almost universal use, because of the high (often unnecessarily high) resolution which can be achieved in routine use. Experience of the expected levels of instrument and sample reproducibility is the best prophylactic against the discovery of non-existent polymorphs or the disregard of actual polymorphs.

27. When comparing IR spectra of suspected polymorphs (or of any organic compounds for that matter), it is important to compare the complete spectra, not just selected peaks. This is particularly true when the spectra have been generated by

different instruments and/or when the spectra have been run at varying instrumental settings, including "resolution" and "transmittance."

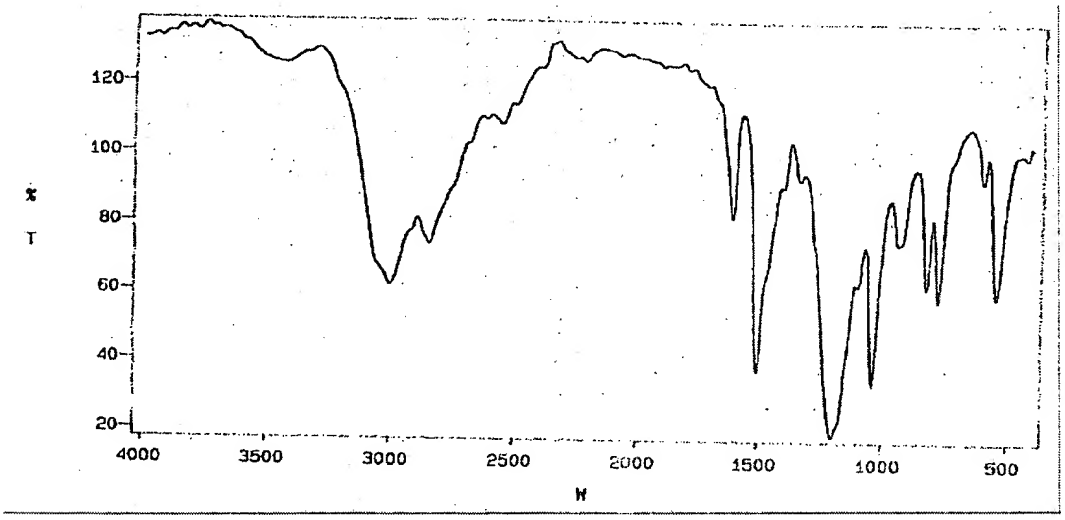
28. Resolution is the ability to differentiate between overlapping peaks. It is a parameter selected by the instrument operator at the time of data acquisition. Resolution is generally stated as a wavenumber value, *e.g.*, 4 cm^{-1} or 8 cm^{-1}, in which no more than a single discrete peak is distinguishable. For example, if two peaks in a hypothetical spectrum are separated only by 6 cm^{-1}, only one peak would be observed if the instrument resolution is set at 8 cm^{-1}. On the other hand, both peaks would be observed if the instrument resolution is set at 4 cm^{-1}. As resolution increases, the overlapping peaks become distinct, but the overall look or appearance of the spectrum remains similar, for example, with regard to the location and intensity of peaks.

29. Resolution must be distinguished from "accuracy." Accuracy is the degree of agreement, stated as a wavenumber difference, between a specific measured peak value in the spectrum of a sample and the corresponding peak value in the spectrum of the authentic standard material. Resolution nevertheless has an effect upon the accuracy of a measured peak value, because use of higher resolution conditions permit a more accurate determination of peak values.

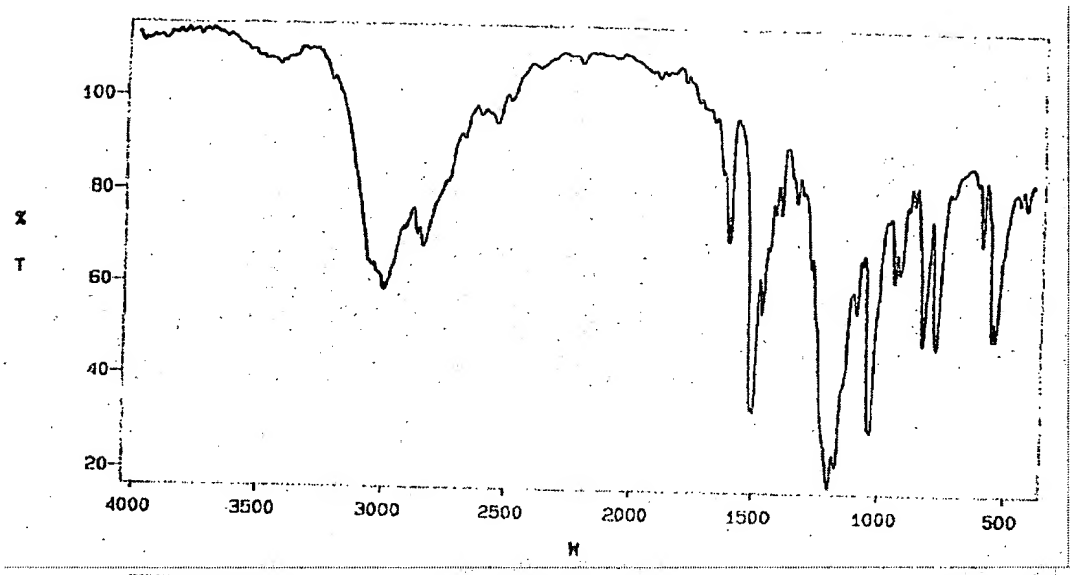
30. Numerical values for peaks appearing in an IR spectrum may be estimated by hand measurement, by approximating the middle of a peak relative to a point on the abcissa of the graph, and they may also be generated by a computer linked to the spectrometer. As resolution increases, the accuracy of a measured peak value increases, because peaks become narrower and better defined.

31. The transmittance tolerance of a spectrometer is an instrumental recognition factor which may be chosen by the instrument operator to increase or decrease the total number of IR peaks identified and printed by the instrument. It is common practice to adjust the transmittance tolerance or threshold of a spectrometer in such a way that only the most intense peaks are identified and printed as numerical peak values, even though the actual number of peaks for the material may be many times greater.

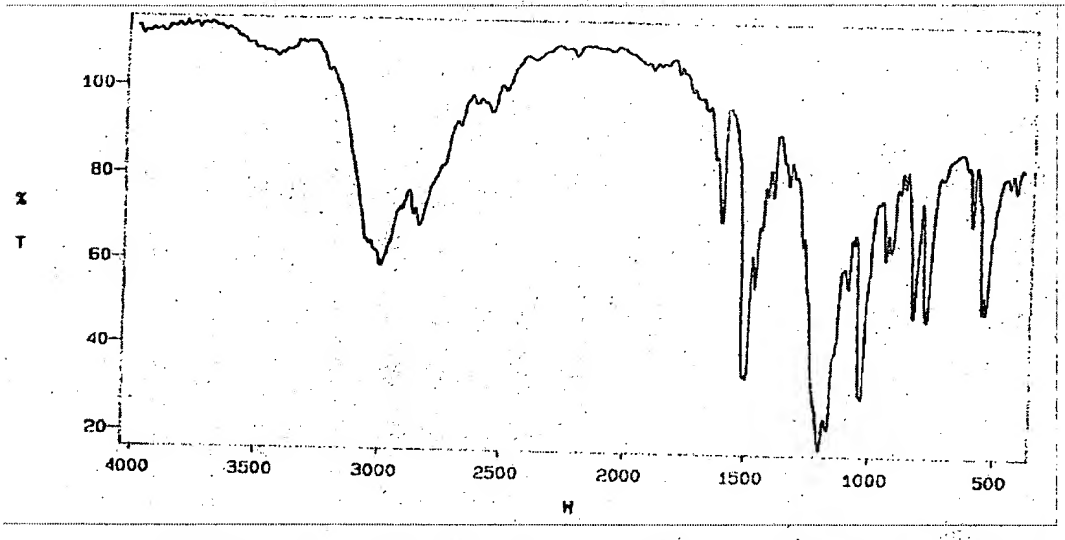
32. The limitations inherent in IR comparisons are illustrated by the five IR spectra below. Each spectrum was derived from the same crystalline material, a pharmaceutical grade sample of paroxetine methane sulfonate. The samples were all run as KBr discs on the same spectrometer. The spectra differ only in their resolution, namely 16 cm^{-1}, 8 cm^{-1}, 4 cm^{-1}, 2 cm^{-1} and 1 cm^{-1}.



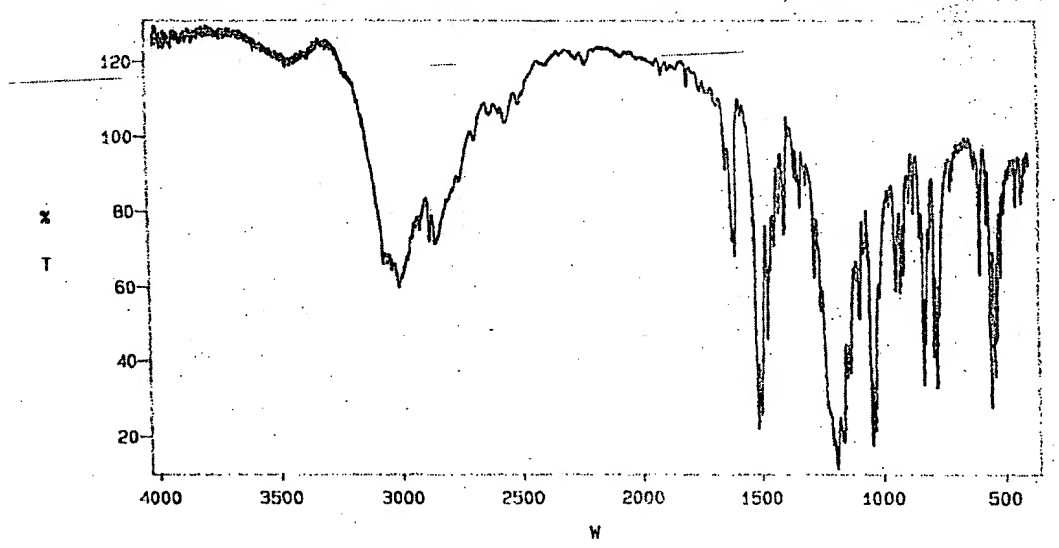
±16 cm^{-1}



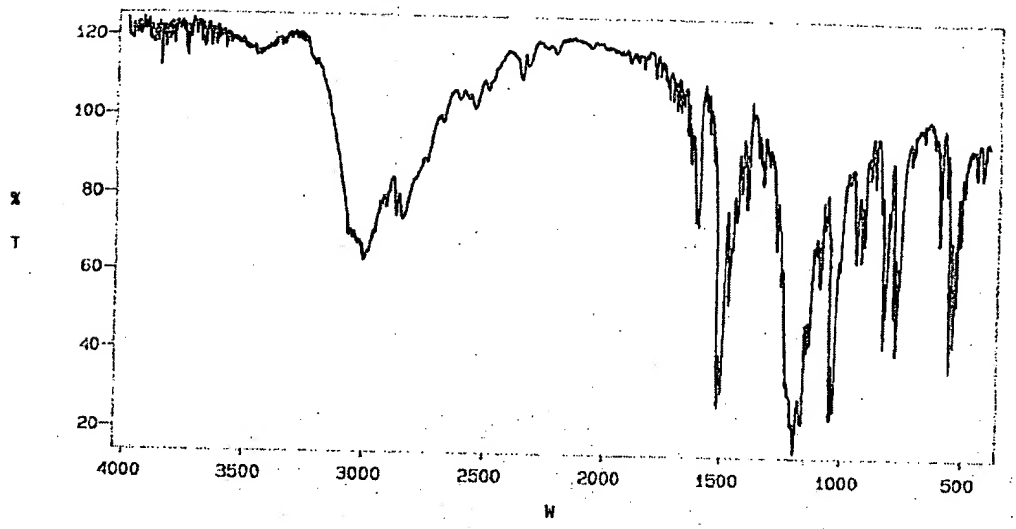
±8 cm^{-1}



±4 cm^{-1}



±2 cm^{-1}



±1 cm^{-1}

33. As seen above, as the resolution increases gradually from 16 cm^{-1} (low resolution) to 1 cm^{-1} (high resolution), the peaks in the spectra become better separated. See, for, example, the absorption appearing in the area at around 1500 cm^{-1}. At the lowest resolution, the absorption band appears as a single peak. As resolution increases, that single peak gradually "divides" into several distinct peaks. Many other areas of the complete spectrum show the same gradual progression, from broad single peaks to several distinct peaks.

34. Depending upon the resolution and method of measurement employed, seemingly dissimilar numerical peak values may be derived from different IR spectra, even though the spectra represent the same material run on the same instrument. One can easily be misled by comparisons of isolated peak values, particularly when they relate to different samples run on different instruments operated under different instrumental parameters. This is why it is important to obtain and overlay and compare <u>complete</u> IR spectra, and not merely compare selected numerical peak values.

The *Crystalline* Paroxetine Methane Sulfonate Described In The Synthon Patent

35. The '447 patent illustrates two syntheses of crystalline paroxetine methane sulfonate. The preparation of a "seeding crystal" of paroxetine methane sulfonate is described in the "Experimental" section, column 7, lines 17-40. A larger scale preparation of crystalline paroxetine methane sulfonate, using the "seeding crystal," is described in Example 1, column 7, lines 44-60. Table 1 of the '447 patent, at column 9, lines 46-58, provides information about the crystalline paroxetine methane sulfonate referenced in Example 1, including proton and C-13 NMR, melting point, DSC melting onset temperature and eighteen IR peaks, *i.e.*, a *partial* list of peaks in the actual IR spectrum.

36. Attached as Tab P is a copy of the actual IR spectrum that was used to derive the IR peaks listed in Table 1 of the '447 patent. The Tab R spectrum was measured using a Unicam Mattsan 500 FT-IR spectrophotometer in a KBr disc (range of 4000-500 cm^{-1}) and the resolution was approximately 8 cm^{-1}.

37. The IR peaks listed in Table 1 of the '447 patent were obtained by *hand measurements* of the Tab P spectrum. When IR peak values are approximated by hand measurement, they can vary by as much as ± 10 cm^{-1}, or even more, particularly at low resolution. Consequently, the peaks listed in Table 1 of the '447 patent were necessarily approximate values and were not as precise as, say, digitally generated peak values, which may have a precision of as little as ± 1 or 2 cm^{-1}, particularly at high resolution.

The *Crystalline* Paroxetine Methane Sulfonate Described In The SKB Patent

38. The '927 patent contains 25 examples which describe the preparation of crystalline paroxetine methane sulfonate. See Tab C, columns 10-16, Examples 1-25. The examples differ with respect to the reagents and manipulative process steps employed to prepare the crystalline material. In particular, various solvents are used (*e.g.*, toluene, tetrahydrofuran, butanone, ethanol, acetone, ethyl acetate, methyl ethyl ketone, butan-1-ol, and propan-2-ol), different stoichiometric amounts of reactants are used and different reaction and crystallization temperatures are used.

39. Notwithstanding that numerous different synthetic and isolation procedures are described in the '927 patent for the preparation of crystalline paroxetine methane sulfonate, the '927 patent identifies only one crystalline form of the material as being obtained. In particular, the '927 patent expressly states that the "same" x-ray powder diffraction pattern and the "same" IR spectrum was generated by the crystalline materials obtained, respectively, in Examples 3, 4, 12, 14, 15, 16, 18, 19 and 20.

40. Attached hereto as Tabs Q and R are copies of IR spectra that SKB submitted to the EPO. Tab S is a summary table SKB submitted to the EPO which lists the numerical peak values from the Tab Q and Tab R spectra. These documents are from the exhibits attached to SKB's Tab G declaration.

41. SKB represented to the EPO that the Tab Q spectrum corresponds to the crystalline paroxetine methane sulfonate described in Example 3 of the '927 SKB patent. As noted on the spectrum, the sample was prepared as a nujol mull, and the

resolution of the spectrograph was 2 cm^{-1}. Thirty-four peak values were selected and printed out, based on the (unstated) transmittance. SKB represented that the Tab R spectrum corresponds to the crystalline paroxetine methane sulfonate described in Example 12 of the '927 SKB patent. As noted on the spectrum, the sample was prepared as a KBr disc and the resolution of the spectrum was 2 cm^{-1}. Forty-eight numerical peak values were selected and printed out.

"SKB's" Crystalline Paroxetine Methane Sulfonate Is The Same Crystalline Paroxetine Methane Sulfonate Described In The Synthon Patent

42. As discussed above, ¶22, powder x-ray diffraction is dispositive evidence of crystalline structure. In his Declaration dated January 17, 2001, Dr. Michael T. Crimmins explains that he made crystalline paroxetine methane sulfonate according to two different procedures described in the '447 Synthon patent and that the powder x-ray diffraction pattern of each of those materials is the same as the powder x-ray diffraction pattern of the crystalline paroxetine methane sulfonates described in the '927 SKB patent. In addition, Dr. Crimmins explains that the materials he made exhibit the same IR spectrum as the spectra of the crystalline paroxetine methane sulfonates described and recited in the claims of the '927 SKB patent. Dr. Crimmins' x-ray diffraction patterns and IR spectra establish that the crystalline paroxetine methane sulfonate described in the '447 patent is the same crystalline paroxetine methane sulfonate later described in the '927 SKB patent.

43. SKB's '927 patent itself implicitly shows that crystalline paroxetine methane sulfonate does not exist in different polymorphic forms. As noted above, ¶ 23, Byrn *et al* [Tab M at 946] specifies that "[t]he first step in the polymorphs decision tree is

to crystallize the substance from a number of different solvents in order to answer the question: Are polymorphs possible?... The solids produced are analyzed using x-ray diffraction and at least one of the other methods." Consistent with the Byrn method, the '927 patent describes numerous different procedures for making and isolating crystalline paroxetine methane sulfonate, including the use of many different crystallization solvents, and then reports the powder x-ray diffraction patterns and IR spectra for the solids produced. As noted above, ¶¶ 37-38, the '927 patent states that the x-ray powder diffraction pattern of each crystalline material was "the same" and also states that the IR spectrum of each crystalline material was "the same." If different polymorphic forms of crystalline paroxetine methane sulfonate existed, it would be expected that they would have been revealed in SKB's numerous experiments.

44. Example 15 of the SKB patent describes crystallization of paroxetine methane sulfonate from *ethyl acetate,* the same solvent from which paroxetine methane sulfonate was crystallized as described in the two synthetic procedures set forth at column 7 of the '447 Synthon patent. For the reasons discussed above, it would be expected that recrystallization of the same dissolved material from the same solvent would produce the same crystalline form of the material, and would not produce different polymorphic forms of that material. This is itself evidence that the Synthon '447 patent and the SKB '927 patent describe the same crystalline paroxetine methane sulfonate.

45. The IR data discussed above, including SKB's, are consistent with the conclusion that the Synthon patent and the SKB patent describe the same crystalline

paroxetine methane sulfonate. SKB simply claimed selectively chosen IR peaks to create the illusion of a difference.

46. Claim 1 of the '927 patent reads "paroxetine methane sulfonate in crystalline form having the following characteristic IR peaks: 1603, 1194, 1045, 946, 830, 601, 554 and 539 ±4 cm^{-1}." As an initial matter, there is no legitimate scientific basis for SKB's selective recitation of these particular peaks. Many other unrecited peaks appear in all of SKB's spectra. More than thirty peaks are listed in Examples 3 and 4, and Examples 4, 12, 14, 15, 16, 18, 19 and 20 repeatedly state, without providing a list of peaks, that "the same" IR was obtained as in Example 3.

47. That SKB's selection of peaks to be recited in its claims was arbitrary, and not based in science, is clear from the fact that two of the ten originally recited peaks were canceled from the claims. As discussed above, the two peaks were evidently deleted solely because there were corresponding peaks listed in the '447 Synthon patent/PCT counterpart. See Tabs I and J. The eight peaks recited in the '927 claims thus represent not only an arbitrary list, but an incomplete list, of all the IR peaks appearing in SKB's spectra.

48. The table below compares the ten peaks originally recited in SKB's claims and the closest "corresponding" peaks listed in Table 1 of the '447 Synthon patent.

SKB '927 Claim 1	Synthon Table 1	Variance (±)
1603 ±4 cm^{-1}	1615 cm^{-1}	12 cm^{-1}
1513 ±4 cm^{-1} (deleted)	1515 cm^{-1}	2 cm^{-1}
1194 ±4 cm^{-1}	1208 cm^{-1}	14 cm^{-1}

SKB '927 Claim 1	Synthon Table 1	Variance (±)
1045 ±4 cm^{-1}	1038 cm^{-1}	7 cm^{-1}
946 ±4 cm^{-1}	931 cm^{-1}	15 cm^{-1}
830 ±4 cm^{-1}	838 cm^{-1}	8 cm^{-1}
776 ±4 cm^{-1} (deleted)	777 cm^{-1}	1 cm^{-1}
601 ±4 cm^{-1}		
554 ±4 cm^{-1}	546 cm^{-1}	8 cm^{-1}
539 ±4 cm^{-1}	531 cm^{-1}	8 cm^{-1}

49. As shown above, six out of the ten peaks initially recited in the SKB claim are listed in the Synthon patent and they match to within ±1 cm^{-1} to ±8 cm^{-1} , within the ±10 cm^{-1} variation the USP states may be expected. Two of the peaks, those deleted from the SKB claim, match to within ±1 or ±2 cm^{-1}.

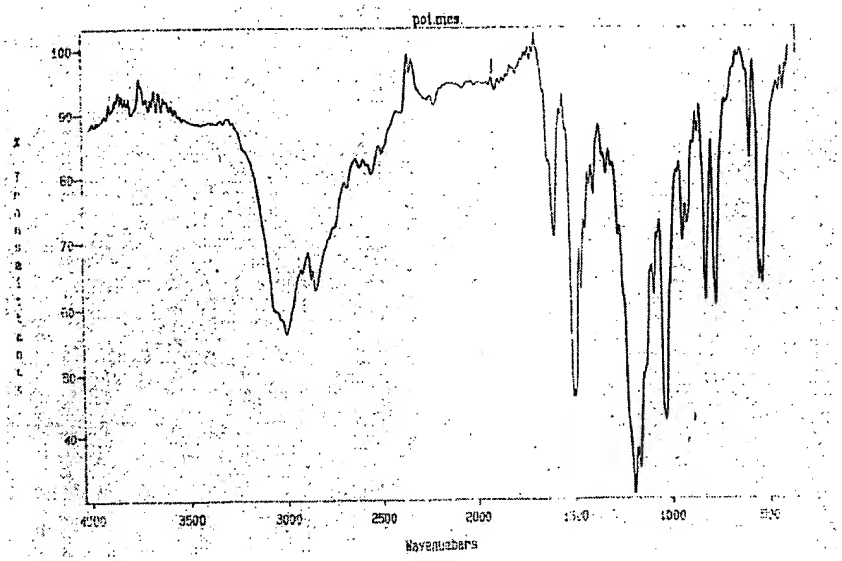
50. The remaining four peaks recited in claim 1 of the '927 patent *appear* to be different from the Synthon peaks, but the differences are artificially created by SKB's arbitrary selection and recitation of those particular peaks, rather than other peaks which also appear in SKB's actual spectra. For example, the SKB claim recites a peak at 1603 cm^{-1}, but it does not recite the peak at 1614 cm^{-1} which *also* appears in the actual SKB spectrum. See Examples 3 and 12 of the '927 patent. The recited peak at 1603 cm^{-1} thus *appears* to differ by 12 cm^{-1} from the 1615 cm^{-1} peak listed in Synthon's Table 1, but the "difference" shrinks to only 1 cm^{-1} if the 1614 cm^{-1} peak is substituted for the arbitrarily recited 1603 cm^{-1} peak. Similarly, SKB's recited peak at 946 cm^{-1} appears to differ by 15 cm^{-1} from the 931 cm^{-1} peak listed in Synthon's Table 1, but the "difference" shrinks to only 4 cm^{-1} if the 946 cm^{-1} peak is replaced by the 927 cm^{-1} peak which *also* appears in SKB's actual spectra.

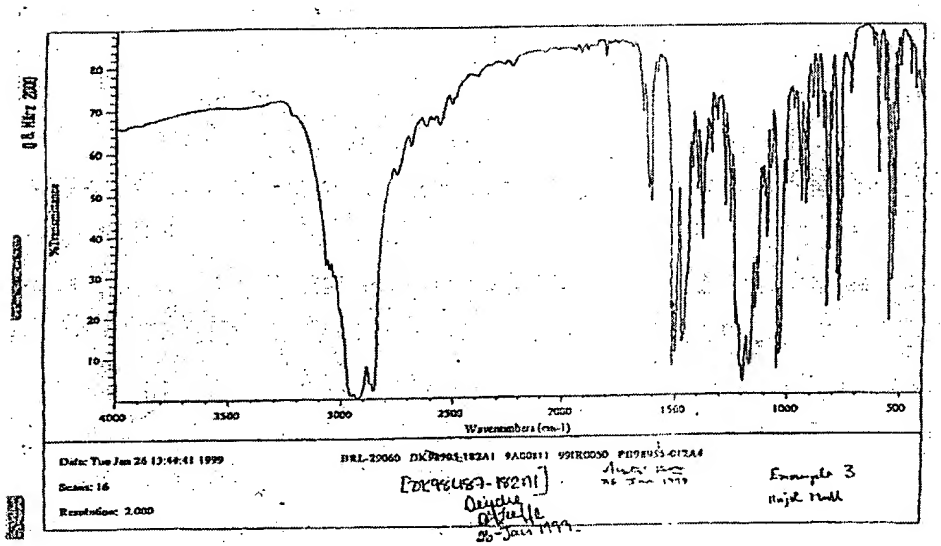
51. The scientific illegitimacy of basing a conclusion of polymorphism upon a comparison of arbitrarily selected IR peaks is plainly illustrated by the fact that, according to SKB's approach, one would conclude that the crystalline paroxetine methane sulfonates described in the '927 patent are *different* -- contrary to SKB's repeated statements in the '927 patent that they have "the same" x-ray powder diffraction patterns and "the same" IR spectra.

52. As discussed above, ¶ 15, SKB submitted IR spectra [Tabs Q and R] and a related peak table [Tab S] corresponding to the crystalline paroxetine methane sulfonates of Examples 3 and 12. The spectra and table listed thirty-four peaks for the Example 3 material and forty-eight peaks for the Example 12 material. Applying SKB's method of comparison, one would conclude that the IR "spectra" from Examples 3 and 12 are different, because some of the peaks listed in Example 12 peaks are not "found" in Example 3. Applying SKB's method of comparison, one would conclude that the respective crystalline materials are therefore different, but that conclusion is untrue, as shown above by the accurate statements in the SKB patent that the IR spectra are "the same" and the x-ray powder diffraction patterns are "the same" for the Example 3 and Example 12 materials. As explained above, ¶¶ 22-23, x-ray powder diffraction is dispositive of the crystalline structure of a material.

53. Simply because a particular numerical peak value is not *listed* in SKB's patent claim - or in Synthon's Table 1 - does not mean that the peak does not appear in the actual spectrum. This is why, see ¶ 33 above, it is important to overlay and compare complete IR spectra, not to just compare selected numerical peak values

derived from incomplete lists. Reproduced below, respectively, is the IR spectrum corresponding to the crystalline paroxetine methane sulfonate of Example 1 of the '447 Synthon patent [Tab R] and the IR spectrum corresponding to the crystalline paroxetine methane sulfonate of Example 3 of the '927 SKB patent [Tab S]:





54. As noted above, ¶¶ 35-36, the Synthon spectrum was obtained at low resolution, 8 cm^{-1}, and the eighteen peak values listed in the '447 patent were

estimated by hand measurement. The SKB spectrum, by contrast, was run at high resolution, 2 cm^{-1}, and the peak values listed in the '927 patent were measured by computer. Notwithstanding these differences, when the complete Synthon spectrum is compared to the complete SKB spectrum it is seen that the overall character of the spectra are equivalent. Peaks corresponding in location and relative intensity are easily seen. No unique peak appears in either spectrum. Upon increase in resolution, the upper [Synthon] spectrum would gradually become more defined and would ultimately look exactly like the lower [SKB] spectrum. This is precisely what is seen in the different resolution spectra presented in the Declaration of Dr. Michael T. Crimmins. See particularly ¶ 11 and related Exhibits E and G (8 cm^{-1} and 2 cm^{-1} resolution) and Exhibits H and J (same) which relate, respectively, to the crystalline paroxetine methane sulfonate made according to the "seed" and "Example 1" procedures described in the Synthon '447 patent.

55. Based on the foregoing facts, the crystalline paroxetine methane sulfonate described in the Synthon patent is the same crystalline paroxetine methane sulfonate later described in the SKB patent.

56. I further declare that the above statements are true and that all statements made upon information and belief are believed to be true and furthermore that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C. § 1001, and may jeopardize the validity of this application or ~~any patent~~ issuing thereon.

29/01/2001
Date

Theodorus Hendricus A. Peters